

# **Cannabidiol binding and negative allosteric modulation at the cannabinoid type 1 receptor in the presence of delta-9-tetrahydrocannabinol: an *in silico* study**

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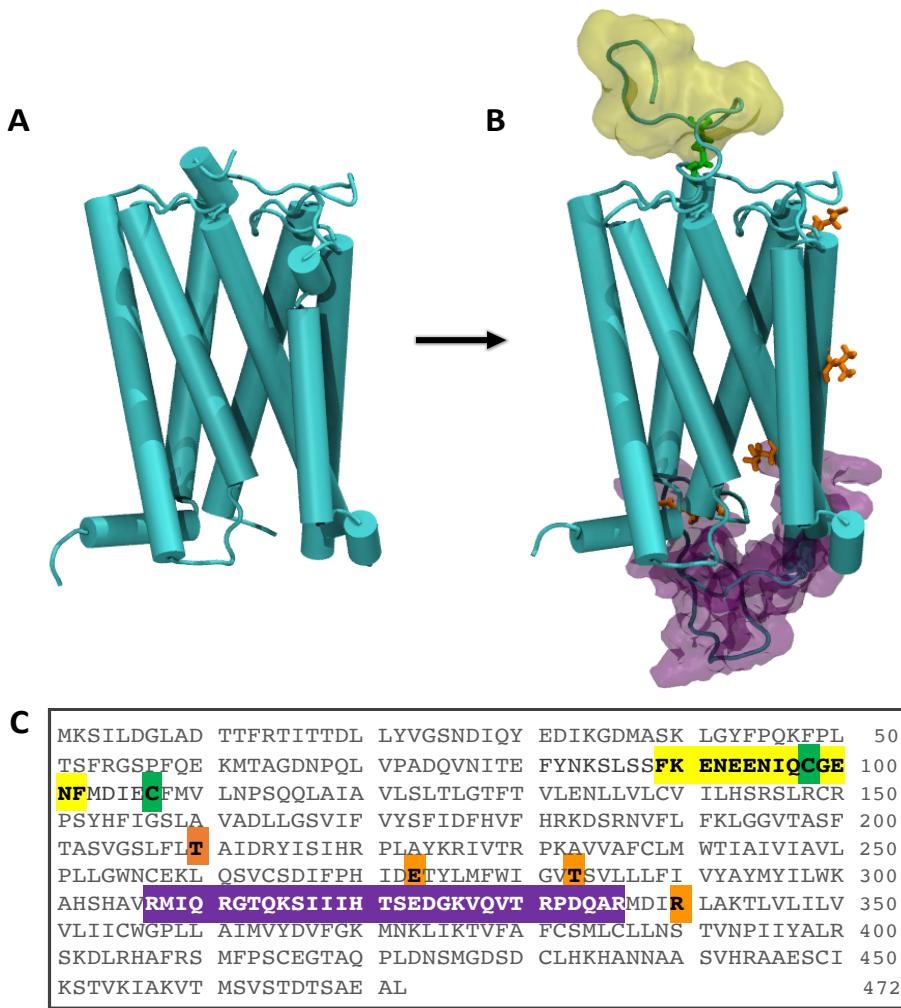
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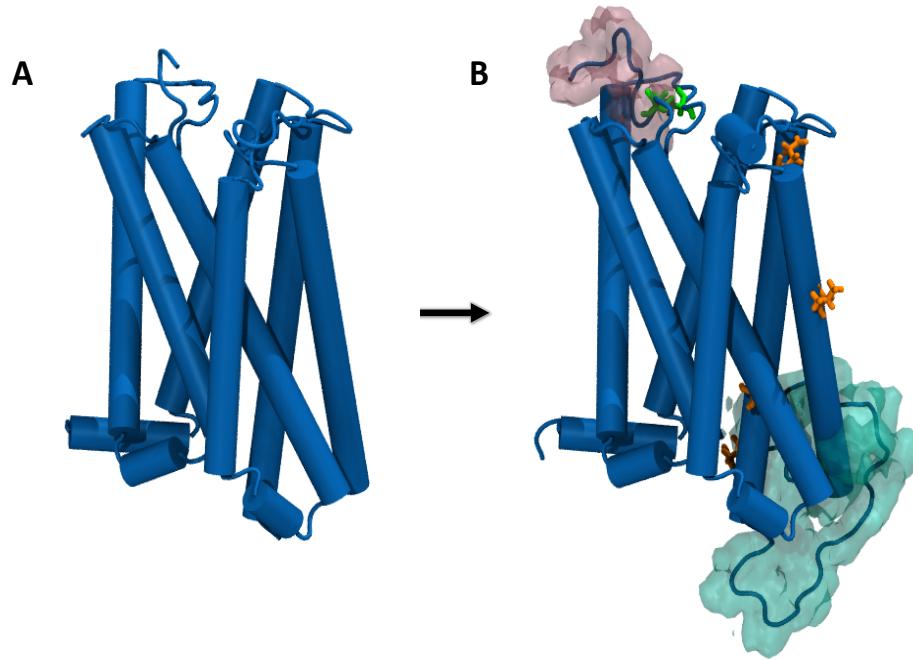
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## **Supporting Information**



**Figure A. Three-dimensional structure of the human CB<sub>1</sub>R in its active conformation.**

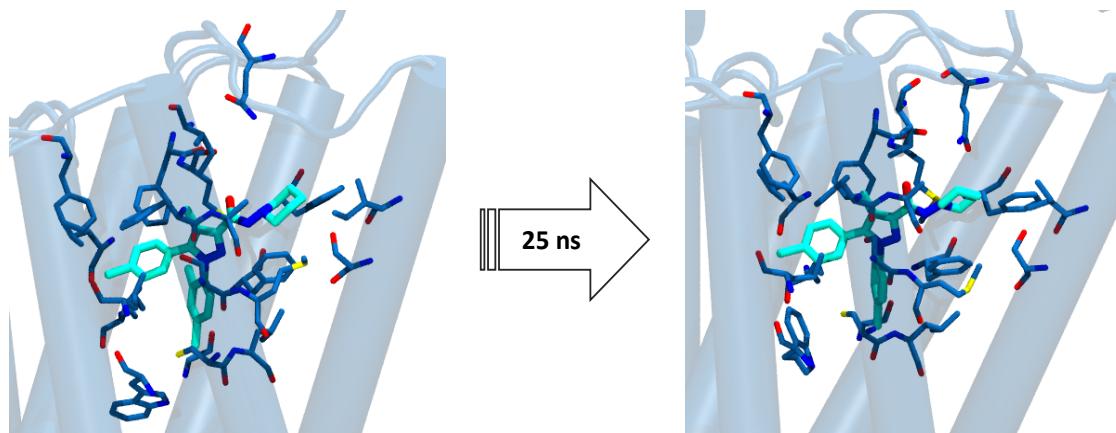
(A) Crystal structure of the CB<sub>1</sub>R bound to agonist PDB: 5XRA. (B) Receptor structure generated by molecular modeling of missing segments. (C) Aminoacidic sequence of the human CB<sub>1</sub>R. Modelled segments are indicated with colors; N-terminal region (yellow), ICL3 (purple), disulfide bridge (green) and mutated residues (orange).



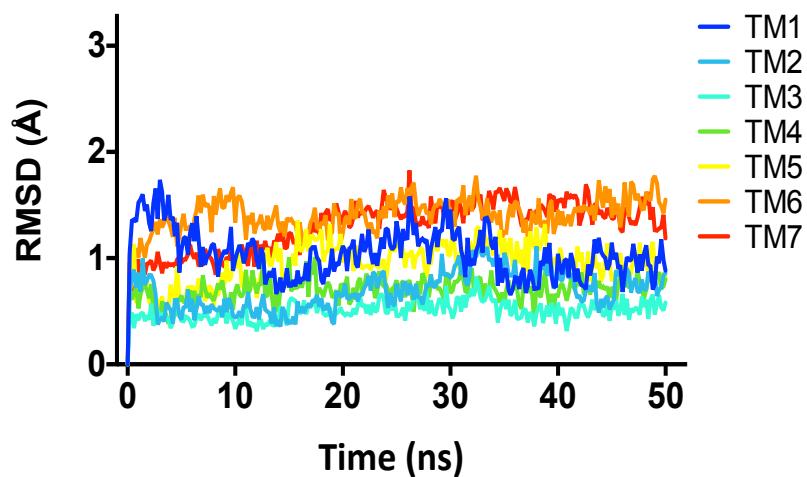
**C**

MKSILDGLAD TTFRTITTDL LYVGNSNDIQQ EDIKGDMASK LGYFPQKFPL	50
TSFRGSPFQE KMTAGDNPQL VPADQVNITE FYNKSLSS <b>FK</b> <b>ENEENIQCGE</b>	100
NFMDIE <b>C</b> FMV LNPSQQLAIA VLSLTLLGTFT VLENLLVLCV ILHSRSILRCR	150
PSYHFIGSLA VADLLGSVIF VYSFIDFHVF HRKDSRNVFL FKLGGVTASF	200
TASVGSLFL <b>T</b> AIDRYISIHR PLAYKRIVTR PKAVVAFCLM WTIAIVIAVL	250
PLLGNCEK <b>L</b> QSVCSDFPH IDE <b>T</b> YLMFWI GVT <b>T</b> VLLLEI VYAYMYILWK	300
AHSHAV <b>RMIQ</b> <b>RGTQKSIIIH</b> <b>TSEDGKVQVT</b> RPDQARMD <b>R</b> LAKTLVLILV	350
VLIICWGPLL AIMVYDVFGK MNKLIKTVFA FCMSLCLLN S TVNPIIYALR	400
SKDLRHAFRS MFPSCETAQ PLDNNSMGDSD CLHKHANAA SVHRAAESCI	450
KSTVKIAKVT MSVSTDTSAE AL	472

**Figure B. Three-dimensional structure of the human CB<sub>1</sub>R in its inactive conformation.** (A) Crystal structure of the CB<sub>1</sub>R bound to antagonist PDB: 5TGZ. (B) Receptor structure generated by molecular modeling of missing segments. (C) Aminoacidic sequence of the human CB<sub>1</sub>R. Modelled segments are indicated with colors; N-terminal region (magenta), ICL3 (cyan), disulfide bridge (green) and mutated residues (orange).



**Figure C. Binding interactions of rimonabant in the inactive conformation of the CB<sub>1</sub>R after 25 ns of simulation.** The orthosteric ligand rimonabant and nearby residues (<5 Å) are shown in cyan and blue sticks respectively.



**Figure D. Plot of RMSD values for each TM helix in the active conformation of the CB<sub>1</sub>R.**

**Table A. Volume of the identified binding sites in the CB<sub>1</sub>R bound to agonist and to antagonist.**

Identified binding site	Volume (Å <sup>3</sup> )	
	CB <sub>1</sub> R-agonist	CB <sub>1</sub> R-anantagonist
S1	909,89	1508,47
S2	500,35	336,77
S3	618,94	Not identified

**Table B. Lowest binding energies of the docking conformations obtained for CBD in the CB<sub>1</sub>R.**

Ligand	CB <sub>1</sub> R	Binding Energy (kcal/mol)
CBD	Active conformation bound to THC	-6,09
CBD	Inactive conformation bound to rimonabant	-7,88